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CONCENTRATION DEPENDENT ACTIONS OF GLUCOCORTICOIDS ON NEURONAL VIABILITY AND SURVIVAL

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□ A growing body of evidence based on experimental data demonstrates that glucocorticoids (GCs) can play a potent role in the survival and death of neurons. However, these observations reflect paradoxical features of GCs, since these adrenal stress hormones are heavily involved in both neurodegenerative and neuroprotective processes. The actual level of GCs appears to have an essential impact in this bimodal action. In the present short review we aim to show the importance of concentration dependent action of GCs on neuronal cell viability and cell survival in the brain. Additionally, we will summarize the possible GC-induced cellular mechanisms at different GC concentrations providing a background for their effect on the fate of nerve cells in conditions that are a challenge to their survival.

Keywords: Glucocorticoids, Cell survival, Cell death

INTRODUCTION

The glucocorticoids (GCs) secreted from the adrenal cortex (corticosterone in rodents and cortisol in primates including humans) exert a wide range of actions on all cell types in mammals. Among these actions GCs have an essential impact on the cells of the central nervous system as they easily pass through the blood brain barrier and bind to intracellular mineralocorticoid (MR) and glucocorticoid (GR) receptors in neurons and glia (McEwen et al. 1968, Veldhuis et al. 1982, Van Eekelen et al. 1987, Fuxe et al. 1988, Reul et al. 1985, Pearce et al. 1989). In the central nervous system, as classical feedback molecules, glucocorticoids maintain the basal activity of the hypothalamo-pituitary-adrenal (HPA) axis and facilitate the termination of stress-induced HPA activation (Dallman et al. 1987, Whitnall et al. 1993, Sapolsky et al. 1984). Importantly, GCs also influence emotional (Cahill et al. 1995, Roozendaal 1999), and learning and memory processes (Bohus et al. 1975, De Kloet 1999, Hui et al. 2004), and are involved in the coordination of such circadian events as

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the sleep-awake cycle and food intake (Bradbury 1998, Dallman 1995). Beside these actions on behavioral brain functions GCs are also known to have a critical impact on neuronal cell survival and viability in conditions that challenge the fate of the nervous tissue e.g. during aging, and in neurodegenerative disease conditions (Abraham et al. 2001, Yusim et al. 2000, Sapolsky 1996).

In the last decades clinical observations pointed out that elevated GC concentrations and/or changes in the daily profile of GC release provide a clinical background to the pathogenesis of endocrine and psychiatric disorders [e.g. Cushing's disease, depression, post-traumatic stress disorder (PTSD)] as well as neurodegenerative diseases like Alzheimer's and Parkinson's disease (AD and PD) and cerebral ischemic stroke (Sapolsky 1996, Weiner et al. 1997, Hartmann et al. 1997, Smith et al. 2002). On the other hand, a fine-tuned action of GCs is essential for neural development and for the maintenance of neural integrity and function in adulthood, as these hormones exert neuroprotective roles in adult brain in a certain concentration-window (Sloviter et al. 1989, Trejo et al, 1995, Abraham et al. 1997, 2000). More recent experimental findings clearly demonstrate that GCs are a major factor in new cell proliferation and neurogenesis in the adult brain.

The concentration of GCs appears to be pivotal in their action on cells. Importantly, most of the vertebrate corticosterone and/or stress experiments on the central nervous system were performed on rodents (especially on rats), although some work was also done on primates (Sapolsky 1990, Sanchez et al. 2000). An overall conclusion from the literature is that the physiological plasma corticosterone concentration range in rats is roughly between 20-50 nM, while elevated levels in rodents from 100 nM and higher may be considered as 'stress' levels of this hormone (Abraham et al. 1998, 2001). Excessive or overexposure of GCs start at 200 nM concentrations or even higher. In the mechanisms of GC-induced changes to the nervous tissue an obvious concentration-related parameter is the duration of the GC exposure. While a transient elevation of stress-induced corticosterone concentration may last at least 1 hour, GC overexposure associated with pathogenic mechanisms can be defined as the sustained high concentration of corticosterone lasting for at least one week (Luine et al. 1994, Watanabe et al. 1992). To explore the effects of corticosterone on the other end of the concentration scale in experiments with rodents, bilateral adrenalectomy (ADX) can be a useful in vivo method to observe and study neurodegenerative processes in animals with a total lack of corticosterone.

In the present communication we will shortly review the strikingly potent role of different GC concentrations in the GC-induced bimodal type of action on neuronal cell survival and viability. In addition, the possible underlying mechanism of action will be discussed.

1. EFFECT OF DIFFERENT CONCENTRATIONS OF GCS ON NEURONAL CELL VIABILITY

The effects of adrenalectomy on the hippocampus in rodents can now be regarded as classical data, where ADX results in the loss of granule cells of the dentate gyrus (DG), by way of detrimental mechanisms resembling cellular hallmarks of neuronal apoptosis (Sloviter 1989, 1993). In some experiments, however, where a lack of DG cell pathology was observed after ADX, this effect could be explained by the existence of extra-adrenal ectopic tissue or incomplete adrenalectomy secreting detectable amounts of GCs (Jaarsma et al. 1992, Sloviter 1993). These findings at least demonstrated the difference between a very low GC level and a total absence of GC in neuronal survival and addresses the role of GC in the very low concentration range.

On the other hand, stress level or overexposure of GCs, similarly to the ADX-induced effect -, may cause neurodegenerative changes in the central nervous system which shows the "whip-saw"- nature of action of GCs on neuronal cell survival. Experiments conducted in various laboratories indicated that a 12-hour/day overexposure to corticosterone for 3 months resulted in a ~20% loss of hippocampal neurons (Sapolsky 1985, Arbel et al. 1994, Clark et al. 1995). Interestingly, these GC-induced exacerbations do not show any apoptotic features appearing in *in vitro* investigations in hippocampal tissue cultures (Roy and Sapolsky 2003). However, others failed to show significant loss of neurons in tree shrews after applying similar high doses of corticosterone, which suggests that a possible strain and species dependency exists in GC-induced neurodegeneration (Vollmann-Holsdorf et al. 1999).

It is worth noting the neuroanatomical consequence of these data, as the hippocampus appears to be the most affected forebrain area where lack of - or direct exposure to elevated concentrations of GCs induces the most outspoken neurodegenerative processes (Arbel et al. 1994, Clark et al. 1995, Dachir et al. 1993). In fact, the hippocampus is the principal extrahypothalamic target of GCs that abundantly expresses both GR and MRs (Veldhuis et al. 1982, Van Eekelen et al. 1987, Fuxe et al. 1988, Reul et al. 1985). However, not the entire hippocampal formation is sensitive to GC overexposure. Pharmacological data demonstrate that high concentrations of GCs are predominantly toxic to pyramidal cells in the CA3 region of the hippocampus (Hibberd et al. 2000, Landfield et al. 1994, Kerr et al. 1994), while damage to CA1 pyramidal cells was less frequently demonstrated (Levy et al. 1994). The reason of this region selectivity is not known, but it is tempting to speculate that CA3 degeneration is a secondary process and results indirectly from GC-induced changes in the functioning and signaling of granule cells terminating on apical dendrites of CA3 pyramidal cells (Patchev 1999). In contrast to the effects of high or low GC concentration, physiological or only slightly elevated GC

levels fail to have any deleterious effect on neuronal cell viability in any animal model investigated so far (Abraham et al. 2001).

Last but not least, the direct GC-induced neuroprotective/neurodegenerative action and their concentration dependence, has potentially major consequences for the human brain. In general terms, exogenous administration of GCs is an effective strategy in clinics to suppress inflammatory reactions in neurological disorders like multiple sclerosis, traumatic brain injury and spinal cord injury. However, the concentration of GCs and the duration of treatment is a critical factor in the clinical practice as well. Regarding the ADX-induced neuronal loss, although a rare condition in humans, there is some human relevance for such effects since a case report indicated selective loss of granule cells in a female patient with adrenocortical deficiency syndrome (Maehlen et al. 1990). It is well known that the physiological or a temporarily elevated GC concentration is more likely to be beneficial than harmful in humans and at those concentrations GCs preserve the physiological metabolism of the neurons and regulate the normal activity of the HPA axis. However, recent pharmacological evidence indicates that chronic administration of the GR agonist dexamethasone - as part of the anti-inflammatory therapy for rheumatoid arthritis - leads to widespread neuronal atrophy in the brain (Benston et al. 1978, Hoogervorst 2002). Similarly, results of clinical studies lend support to the notion that overexposure of the endogenous plasma corticosterone levels may be regarded as a major risk factor for neurodegenerative disorders in the human brain in particular when present or applied in combination with other jeopardizing conditions (Sapolsky 1996). This notion is further supported by the observation that patients with AD and PD exhibit significantly higher total plasma cortisol concentrations, whereas the diurnal variation of cortisol secretion did not differ from healthy controls (Hartmann et al. 1997, Weiner et al. 1997). Moreover, a significant correlation between increased plasma cortisol levels and the degree of mental deterioration and decreased volume of the hippocampus was demonstrated in AD patients (De Leon et al. 1988). Based on clinical and experimental investigations, a working hypothesis suggests that a high GC concentration might be a key factor in the loss of dopaminergic neurons that underlies PD (Smith et al. 2002). In endocrinological disorders such as Cushing's syndrome it is the high plasma cortisol concentration that may deteriorate the function and structure of the central nervous system. In fact, clinical studies demonstrated a reduced volume of the hippocampus and impaired cognitive function correlating with an increase in plasma cortisol levels in patients with Cushing's syndrome (Starkman 1992, 2003). It is worth noting that the normalization of cortisol levels in Cushing's disease decreases the hippocampal atrophy indicating a partly reversible effect of high cortisol in neuronal integrity (Starkman 1999). In addition, there is evidence that

supports high GC concentrations as a predisposition factor in the pathogenesis of psychiatric affective disorders, such as major depression and PTSD. The impaired function of the hippocampus appears to play a pivotal role in the manifestation of major depression (Lee et al. 2002). Since the cortisol level is elevated in patients with major depression, it is tempting to speculate that the threat to hippocampal neurones by high cortisol might lead or add to the manifestation of the disease. This working hypothesis is supported by a clinical study where the hippocampal volume in individuals with major depression exhibited pronounced negative correlation with the plasma concentration of cortisol (Sheline 1996). It should be noted, however, that the rather minimal cell loss in the hippocampus does not have a predominant role in this reduction of hippocampal volume (Gurvits et al. 1996, Lucassen 2001) and that hippocampal volume reduction should be attributed to tissue shrinkage and probably dendritic atrophy. In this respect it is noteworthy that some patients with major depression showed a strong astrocytic reaction and enhanced synaptic reorganization in the hippocampus (Muller et al. 2001). Interestingly, patients with PTSD also exhibit a reduced volume of the hippocampus even without cortisol hypersecretion (Gurvits et al. 1995, Bremner et al. 1995). This fact clearly indicates episodic stress and/or temporary hypersecretion of cortisol, which might elicit irreversible changes in susceptible brain structures and potentially lead to the subsequent manifestation of PTSD.

Summarizing these facts, an obvious conclusion that can be drawn based on literature reports is that the concentration of GCs is a critical factor in the neuronal viability. Both lack and overexposure or prolonged administration of GCs increases the possibility of neurodegenerative processes. In contrast, the physiological or slightly elevated concentration of GCs preserves the integrity of neuronal cells.

2. IMPACT OF DIFFERENT GC CONCENTRATIONS ON NEURONAL CELL SURVIVAL AT DIFFERENT NOXIOUS STIMULI

Besides the direct action of different concentrations of GCs on neuronal cellular vitality and survival, variations in GC concentrations effectively alter the neuronal responses under noxious conditions as well.

ADX enhances the vulnerability of neurons to excitotoxic insults which is the case in ischemic stroke and Alzheimer's disease, but probably to other well known neurodegenerative disorders as well. In this regard, recent studies in the authors' laboratories demonstrated that ADX and very low corticosterone concentrations significantly potentiated β-amyloid (Aβ)- and N-methyl-D-aspartate (NMDA)-induced excitotoxicity to cholinergic neurons of the rat magnocellular nucleus basalis (Abraham et al. 2000).

Similar to ADX, the overexposure of GCs can endanger neurons again via enhancing their vulnerability of nerve cells to neurotoxic insults (Sapolsky and Pulsinelli 1985). In this regard, stress levels of corticosterone were demonstrated to increase neuronal damage in the hippocampus following acute hypoxia/ischemia in both rats and gerbils, as well as to aggravate the effect of hypoglycemia in hippocampal tissue explants (Kide et al 1986, Morse et al. 1990, Yusim et al. 2000). Moreover, stress levels of corticosterone contribute to the augmentation of neuronal loss induced by a variety of neurotoxins, like NMDA, Aβ (Abraham et al. 2000), kainic acid (Sapolsky 1986), 3-acetylpiridine (Sapolsky et al. 1985), and ethylcholine aziridinium (Hortnagl et al. 1993, Amoroso et al. 1993). Interestingly, in some cases the deleterious effect of GCs can be outweighed by certain metabolic conditions, leading to neuroprotection. Accordingly, despite sustained elevated corticosterone concentrations, caloric restriction decreases the risk of GC-induced neurodegeneration and increases the resistance of neurons to toxins and injury (Patel and Finch, 2002).

On the other hand, corticosterone itself has neuroprotective potential against excitotoxic insults at slightly elevated concentrations. Corticosterone concentrations ranging from 20-270 nM in blood plasma profoundly attenuate both NMDA and Aβ toxicity on cholinergic neurons of the rat magnocellular nucleus basalis (Abraham et al. 2001). In addition the slightly elevated and stress levels of GCs as most powerful immunosupressors play a major role in protecting the brain against immunochallenge such as exposure to bacterial cell wall components (Nadeau and Rivest 2003).

Taken together, similar to the GC-induced action on neuronal viability corticosterone has a bi-directional effect on neuronal survival as indicated by various studies including our own experimental observations. This bidirectional effect becomes apparent in the U-shaped profile of a dose-response relationship between plasma corticosterone concentration and the extent of damage to cholinergic basal forebrain neurons (Abraham et al. 2001). Whereas ADX (eventual loss of serum corticosterone), and highly elevated corticosterone concentrations (310-650 nM) potentiate both NMDA- and Aβ-triggered excitotoxicity, moderate levels of plasma corticosterone in a narrow concentration window exert significant protection against excitotoxic neuronal damage (Abraham et al, 2001).

3. THE IMPACT OF DEVELOPMENT AND AGEING IN GC-INDUCED NEURODEGENERATIVE/NEUROPROTECTIVE ACTION AT DIFFERENT GC CONCENTRATIONS

During the perinatal period, a constant basal level of GCs is essential for normal development of the CNS (Gould et al. 1997). Accordingly, birth and death of granular cells of the dentate gyrus appears to be reg-

ulated by GCs. Their pivotal role during development is further supported by experimental studies reporting protective effects of dexamethasone in a neonatal model of hypoxic-ischemic brain injury (Tuor et al. 1993, 1995). Also considering the fact that lack of corticosterone induced apoptosis in dentate gyrus, Sloviter and colleagues postulated that GCs are protective *'obligatory growth factors'* for hippocampal granule cells (Sloviter et al. 1993). It is worth noting, however, that long lasting neonatal overexposure of GR by dexamethasone induces serious deficits in synaptic plasticity and spatial learning in adulthood (Kamphuis et al. 2003). These experimental results further suggest that the fine-tuned concentration windows of GCs are important in the GC-induced effect on neuronal cell survival during development as well.

In contrast to the enhanced survival potential of neonatal neurons, aging of the brain is associated with the reduced ability of neurons to stabilize their ion (notably the maintenance of Ca^{2+}) homeostasis, and with enlarged ACTH and corticosterone responses to stress, which lead to the enhancement of GC-induced neurodegeneration of nerve cells. Early studies of Landfield and colleagues demonstrated that adrenal hypertrophy and subsequent prolonged hypersecretion of corticosterone positively correlate with increased neuronal damage and appearance of reactive astroglia in the hippocampus during aging (Landfield et al. 1978). Additionally, elevated basal corticosterone levels accelerated hippocampal neuronal damage in aging (Issa et al. 1990). Pharmacological studies demonstrated that antagonism of GR with RU486 significantly attenuated the age-related hippocampal damage (Talmi et al. 1996), while aging exacerbates the dexamethasone-induced apoptosis in the DG (Hassan et al. 1996). Moreover, a continuously elevated amount of corticosterone delivered by means of foot-shocks for 6 months significantly increased hippocampal aging (Kerr et al. 1991).

Taken the above data together ageing slightly modifies the bimodal role of GCs on neuronal cell viability and survival. While GCs are essential to neuronal development, aging increases the neurodegenerative potential of high GC concentrations.

4. POSSIBLE MECHANISMS AT DIFFERENT GC CONCENTRATIONS UNDERLYING THE BIMODAL ACTION OF GCS UPON NEURONAL CELL SURVIVAL AND VIABILITY

In general terms, GCs may have an offensive or a defensive action on neurons leading to consequent neuroprotective or neurodegenerative process. In this paragraph of this review, we aim to shed some light on the mechanisms underlying this bimodal action and the role of different GC concentrations in these mechanisms.

Before starting to discuss the possible mechanisms, we should mention the critical role of distinct classes of corticosteroid receptors in

determining the cellular outcome of GC action on neuronal cell physiology and maintenance of its integrity. Importantly, the MR and GR have a different binding affinity to corticosterone. Binding studies indicate that MR associates with corticosterone with high affinity while GR has a 10-fold lower affinity for corticosterone (De Kloet et al. 1998). Basal corticosterone concentrations saturate the MR binding capacity and GR can be activated in addition to MR when corticosterone levels are high (Reul and De Kloet 1985). Deleterious effects of GCs are mediated by low-affinity GR, which is also evidenced by the pharmacological observation where synthetic GR agonists [e.g. methylprednisolone (Hall et al. 1985, Uhler et al. 1994) and dexamethasone (Koide et al. 1986)] share the ability to cause significant neurodegeneration, whereas non-GR ligands do not have neurodegenerative potential in the brain (Goodman et al. 1996, Packan et al. 1990). These facts are further supported by experiments on Purkinje cells, where the administration of GR antagonist RU486 can effectively protect these cells form apoptotic processes in the cerebellum (Ghoumari et al. 2003). It is worth noting that this effect may be mediated via novel mechanisms and/or unknown variant(s) of GR. Moreover, GR-mediated neuronal loss can be effectively abrogated by the simultaneous activation of the MR, suggesting that MRs mediate neuroprotective effects of GCs (Sousa at al. 1999). Almeida *et al.* (2000) provided further indication on the critical role of MR/GR balance in neuronal survival. In fact, stimulation of GR was shown to lead to neuronal apoptosis by significantly increased expression of the pro-apoptotic molecule Bax, relative to that of the anti-apoptotic molecules Bcl-2, or Bcl-X, whereas opposite, neuroprotective effects were observed following stimulation of MR. Thus the balance of MR/GR in neuronal survival and viability appears to be essential. However, in spite of the concordant experimental data in rodents, studies on primates do not support these findings. Indeed, neuroanatomical investigation reveals a very low level of GRs in the primate hippocampus (Sanchez et al. 2000). These data also suggest that GCs effect is predominantly mediated via MRs in the primate hippocampus.

The metabolic conditions such as the bioavailability of glucose have a pivotal impact on the maintenance of the integrity of neuronal cells. GCs as catabolic hormones can block the uptake and/or the metabolism of glucose and as such threaten fundamental physiological neuronal functions. Besides the GC-induced blockade of transendothelial glucose transport in the brain, GCs have a potential inhibition on glucose uptake in neurons and glia as revealed in the hippocampus (Sapolsky 1996, Doyle 1993). This GC-induced disruption in neuronal glucose utilization and consequent energetic failure in neurons might explain the lack of energy-dependent apoptotic processes following GC overexposure (Roy and Sapolsky 2003). On the other hand, this GC-induced metabolic challenge

is in itself probably insufficient to directly kill the neurones. However, it may effectively contribute to the effect of the high level of GCs on the neuronal cell survival following excitotoxic injury which imposes high demands on available energy in the nerve cells. In contrast, the consequent high corticosterone level following caloric restriction failed to have any deleterious effect on neurons (Patel and Finch 2002). Caloric restriction itself has a neuroprotective effect due to combinations of different mechanisms. In fact, caloric restriction increases the expression of HSP70 and neutrophic factors (e.g. BDNF, NGF) promoting the neuronal survival and plasticity (Patel and Finch 2002). In addition, caloric restriction attenuates the oxidative damage and ROS generation and decreases the glial reaction. According to one hypothesis, these protective effects of caloric restriction simply outweigh the deleterious effect of GCs in the brain (Patel and Finch 2002).

Generally, GABA exerts an inhibitory activity in the brain and thus can be regarded as an intrinsic neuroprotective factor against excitotoxic brain damage. High concentrations of GCs may deteriorate GABAergic neurotransmission in the brain, as they significantly reduce the efficacy of GABAergic signalling by decreasing the binding of GABA, neurosteroids and benzodiazepines to GABA receptors (Acuna et al. 1990; Zeise et al. 1992). In fact, electrophysiological measurements on brain slices support the above findings, as the high GC concentrations highly attenuate the generation of $GABA_A$ receptor-mediated inhibitory post-synaptic potentials (Joels and De Kloet 1993). It has been postulated that GC-induced impairment of GABAergic neurotransmission is probably due to changes in GABA receptor mechanism rather than the GABA release itself. In fact, microdialysis studies in freely moving rats failed to show significant effects of intracerebral GC administration on extracellular GABA concentrations (Abraham et al. 1996; Venero and Borell 1999), suggesting a predominant role of GABA receptors in these mechanisms.

Besides GABA, the other GC-sensitive essential neurotransmitters are the excitatory amino acids (EAA) including glutamate and aspartate. During the past decade an impressive body of evidence emerged on the critical role of GCs in modulating glutamate metabolism and glutamatergic neurotransmission in the brain (Mohaddam 1993, 1994). Importantly, glutamate binds to metabotropic and ionotropic glutamate receptors (e.g. NMDA and AMPA receptors) in the brain. At physiological conditions, the glutamate-induced Ca^{2+} mobilization *via* NMDA receptors leads to the enhancement of synaptic communication in both pre- and post-synaptic elements, and to the formation of highly active perforated synaptic contacts (Edwards 1995). Under pathological conditions, however, excessive glutamate release induces an uncontrolled rise in the intracellular Ca^{2+} concentration in neurons (Szatkowski and Attwell 1994; Schousboe et al. 1997). Accordingly, this circumstance may evoke mito-

chondrial dysfunction, increase in the formation of reactive oxygen intermediates and activation of Ca^{2+}-dependent proteases, NO synthase, lipases and nucleases, leading to neuronal damage (Dugan and Choi 1994). Results of both *in vitro* investigations on cell culture and *in vivo* microdialysis studies showed that high GC concentrations might enhance the neuronal cell vulnerability via excessive glutamate-induced excitoxicity (Abraham et al. 1996; Moghaddam 1993; Stein-Behrens et al. 1994; Semba et al. 1995). Indeed, these experiments clearly demonstrated that overexposure of GCs induces an extracellular glutamate increase in the brain in which the GC-induced inhibition of astrocytic glutamate uptake plays a critical role (Virgin et al. 1992).

Besides the indirect effect of GCs on intraneuronal Ca^{2+} concentrations via enhanced glutamate increase, chronic absence as well as high concentrations of corticosterone may directly modulate Ca^{2+} currents in nerve cells. In fact, within three days following ADX the amplitude of voltage-dependent Ca^{2+} currents significantly increases (Karst et al. 1994), concomitant with a relatively small Ca^{2+}-dependent K^+ conductance in hippocampal neurons (Kerr et al. 1989). Chronic exposure to high corticosterone concentrations affects the Ca^{2+} conductance of neuronal membranes in a similar fashion (Karst et al. 1994). Importantly, a single cell Ca^{2+} imaging study revealed that high corticosterone levels enhance the NMDA receptor mediated intraneuronal Ca^{2+} elevation in the hippocampus (Takahashi et al. 2002). These events become even more deleterious if the age-related elevation of basal GC concentrations is considered (Kerr et al. 1989; Thibault et al. 1996). Molecular biological data further support the direct effects of GCs on Ca^{2+} currents, as high GC concentrations increased the neuronal mRNA content of Ca^{2+} channel subunits in ADX rats, whereas chronic supply with corticosterone in the physiological range reduced Ca^{2+} channel subunit mRNA expression (Nair et al. 1998). Additionally, high concentrations of GCs repress the expression of plasma membrane Ca^{2+} pump isoform 1 mRNA in several brain regions, thereby providing a unique way to reduce Ca^{2+} extrusion from nerve cells (Bhargava et al. 2000). Landfield and his colleagues (1992) postulated that excessive activation of GR and dysregulation of the intracellular Ca^{2+} homeostasis might be two distinct phases of a single process that significantly increases the susceptibility of hippocampal neurons to neurodegeneration during aging and in Alzheimer's disease. There is however a limitation to the applicability of the above hypothesis since the presumed underlying mechanisms were predominantly identified in CA1 neurons. This fact definitely does not allow ready extrapolation of the pharmacological data on high GC-induced neurodegeneration to the DG, CA3 and CA2 regions, or to other brain regions affected in AD. Notably, in spite of the corticosterone-induced increase of high-voltage-activated calcium currents and the expression of the alpha1 subunit of the L-type calcium

channel in principal neurons of the basolateral amygdala, corticosterone failed to have any neurodegenarative effect in this area (Karst et al. 2002).

In this paragraph, it is important to mention an essential pre-receptor mechanism that exists at high levels of GC-induced neurodegeneration. The metabolism of GCs is controlled by tissue-specific enzymes such as 11ß-hydroxysteroid dehydrogenases (11ß-HSD). Importantly, this enzyme has two isoforms: 11ß-HSD2 inactivates cortisol while 11ß-HSD1 is a 11ß-reductase in vivo that acts in many tissues to increase local intracellular glucocorticoid concentrations (Seckl et al. 2001). Since 11ß-HSD1 is predominantly expressed in the hippocampus (Moisan 1990), it may enhance the GC-induced neurodegenerative actions in this region (Rajan et al. 1996).

We have stated above that GCs are the most powerful endogenous immunesupressors especially for the innate immune system. In fact, GCs are potent inhibitors of the transcription of genes encoding proteins involved in the innate immune system, such as nuclear factor κB (NFκB) (McKay et al. 1999). Such immune control of GCs on the innate immune system also exists in the CNS (Nadeau and Rivest 2003). Indeed, following bacterial cell wall component lipopolysaccharide (LPS) administration, the transient elevation of GC concentrations plays a pivotal role in controlling the microglial TNFα production (Nadeau and Rivest 2003). Thus, a transiently elevated GC concentration prevents the brain from the overproduction of neurotoxical TNFα resulting in an essential protection mechanism for neurons against immune challenge (Nadeau and Rivest 2003).

Fine-tuned activation of GR at slightly elevated GC concentration also induce the expression of a broad variety of substances with a neurotrophic potential, such as lipocortin-1 (Flower et al. 1994), basic fibroblast growth factor (bFGF) and nerve growth factor (NGF) (Mochetti et al. 1996). In this regard, lipocortin-1 is known to inhibit the synthesis of prostaglandins and leukotrienes by inhibiting phospholipase A2, the key enzyme of the arachidonic acid cascade, and thereby precludes the subsequent production of potentially cytotoxic oxygen radicals (Flower et al. 1994). In fact, lipocortin-1 acts as a neuroprotective agent against ischemic insults and inhibits neuronal damage induced by infusion of NMDA receptor agonists in the brain (Relton et al. 1991). Regarding bFGF and NGF, *in situ* hybridization studies revealed that corticosterone administration elicits the temporal induction of mRNA coding for both neutrophic growth factors in the cerebral cortex (Mochetti et al. 1996). Conversely, ADX leads to a decreased expression of neutrophins, which may be directly associated with increased neuronal damage following ischemic conditions or hypoglycemic stress (Barbany et al. 1992). Importantly, immobilization stress which results in an overexposure to GCs was reported to block NGF mRNA expression in the hippocampus

(Ueyama et al. 1997), where most of the GC-induced damaging effects occur. Taken together, these result may point to the fact that GCs in a narrow concentration window can activate protective factors such as lipocortin-1, NGF and FGF, but overexposure or lack of GC production may inhibit neutrophin expression and neutrophin linked-signal transduction pathways.

In spite of the complex mechanism of action of GCs on neuronal cell survival and viability, some overall final conclusions can be drawn based on literature reports and our own experimental findings. GCs can activate both neurodegenerative as well as neuroprotective processes. Both the lack or a high concentration of GC may initiate and/or work in concert with endangering mechanisms in neurons, whereas physiological or mildly elevated GC concentrations stimulate defensive molecular events in the central nervous system.

5. SUMMARY

In the present review we provided a survey of evidence showing that physiological levels of GC concentrations provide a balanced milieu for neuronal maintenance while a slightly increased GC levels may even induce neuroprotective processes. In contrast, the lack or high concentrations of GCs may shift this sensitive balance into the neurotoxic range. Importantly, the set point of these concentration-dependent actions of GCs may be different when viewed from the aspect of different brain structures, distinct metabolic conditions or ageing. Although particular cellular mechanisms of GC action are relatively well characterized, a comprehensive and integral understanding of the precise GC concentration-dependent molecular mechanism should be elucidated in the future. As such, further molecular biological studies must reveal how and when a shift from the neuroprotective (physiological) to the neurotoxic effect in the GCs' balance range occurs.

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